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EXAMINER	
ROONEY, NORA MAUREEN	
ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,940	GERACI, DOMENICO	
	Examiner	Art Unit	
	NORA M. ROONEY	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 January 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-44* is/are pending in the application.

4a) Of the above claim(s) *29-36 and 40-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-28,37-39 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 August 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/28/2006 and 09/26/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 23-44 are pending.

2. Applicant's election with traverse of Group I, now claims 23-28, 37-39 and 44, in the replies filed on 07/29/2009 and 01/11/2010 is acknowledged. The traversal is on the ground(s) that "examination of all pending claims would not constitute a serious burden. Although the inventions identified by the Examiner are separately patentable, both the need for compact prosecution and the public interest would be served by examination of all claims in a single application. In particular, the claims of both Groups I and II should be examined in the same application."

This is not found persuasive because the inventions of Groups I and II listed in this action are independent or distinct and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply: (a) the inventions have acquired a separate status in the art in view of their different classification;(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter; (c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries); (d) the prior art applicable to one invention would not likely be applicable to another invention; and (e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 29-36 and 40-43 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 07/29/2009.

4. Claims 23-28, 37-39 and 44 are currently under examination as they read on a fusion protein characterized in that it comprises the amino acid sequences of different allergens belonging to the non-specific Lipid Transfer Protein (ns-LTPs) family, in that said sequences lack one or more of the four disulphide bridges present in the sequences of the wild type allergens, at least one in the amino terminal region comprised between amino acid residues 1 and 30 and in that said sequences maintain essentially the same length as the sequences of wild type allergens, pharmaceutical compositions thereof and methods of preparing a pharmaceutical composition.

5. Applicant's IDS documents filed on 08/28/2006 and 09/26/2006 have been considered.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined

application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 23-28, 37-39 and 44 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 29-33 of copending Application No. 10/557,586 in view of Columbo et al.(IDS filed on 08/28/2006).

Claims 29-33 of U.S. Application 10/557,586 are directed to Parj1/Parj2 multimer proteins comprising mutations. In particular, a multimer protein molecule comprising amino acid sequences SEQ ID NO:4 and SEQ ID NO:2 for medical use as a hypoallergenic agent and a

pharmaceutical composition comprising an effective amount of the multimer protein molecule and suitable adjuvants.

The claimed invention differs from the prior art in the recitation of "said sequences lack one or more of the four disulphide bridges present in the sequences of the wild type allergens, at least one in the amino terminal region comprised between amino acid residues 1 and 30 and in that said sequences maintain essentially the same length as the sequences of wild type allergens" of claim 23; "characterized in that the amino acid sequence of each of the allergens is independently mutated by elimination or substitution of one or more cysteine residues involved in the formation of a disulphide bridge" of claim 24; "characterized in that the amino acid sequence of each of the allergens is independently mutated by elimination or substitution of one or more cysteine residues in positions corresponding to the positions 4, 14, 29, 30, 50, 52, 75 and 91 of the amino acid sequence of Parjl and/or Parj2 allergen" of claim 26; and "characterized in that it contains amino acid sequences of Parjl and Parj2 allergens, both independently modified by substitution of cysteine residues with Asn, Ser, Thr, lie, Met, Gly, Ala, Val, Gln or Leu residues in positions 29 and 30 or 4, 29 and 30 or 29, 30, 50, 52" of claim 27.

Columbo et al teaches that Par j 1 and Par j 2 are the two major allergens in Parietaria judaica pollen which are the main cause of allergy in the Mediterranean. Parietaria pollen also contains at least 7 other minor allergens (In particular, second paragraph on page 2780). Par j 1 and Par j 2 allergens exhibit 45% overall homology and 60% homology in the 1-30 region of the proteins known to have one common, discontinuous IgE epitope (In particular, second paragraph on page 2780, first paragraph on page 2784). Colombo et al teaches Par j 1 and Par j2 allergens with substantially the same sequences as 1-102 of SEQ D NO:4 (Parr j2) and 105-243 of SEQ

ID NO:4 (Par j I). The reference also teaches loop 1 allergen mutants mutated in amino acids 1-30 of 1-102 of SEQ D NO:4 (Parr j2) and 105-243 of SEQ ID NO:4 (Par j I) for diagnosis and therapy of pollen allergy (In particular, pages 199-200 'Materials and Methods', sequences in Table 2, whole document). Columbo et al. teaches that mutation of positions C4, C52, C14, C29, C30 and C75 effect structure alanine leads to a loss of IgE binding in this region (In particular, page 2782 first full paragraph). The reference teaches that the development of hypoallergenic molecules with reduced or eliminated IgE binding can be used in allergen therapies (last paragraph), particularly given the importance of these allergens to allergy in the Mediterranean and throughout the world (In particular, second paragraph on page 2780, last paragraph on page 2784). It is noted that 105-243 of SEQ ID NO:4 (Par j I) is the sequence for Par j1 with C4, C29 and C30 mutated to serine and 1-102 of SEQ D NO:4 (Parr j2) is the sequence for Par j 2 with C4, C29 and C30 mutated to serine.

It would have been obvious to one of ordinary skill in the art at the time of invention to mutate the multimer protein of U.S. Application Number 10/557,586 at the cysteine residues 4, 29 and 30 in both Par j1 and Parj 2 portions to decrease IgE binding for in vivo pharmaceutical use.

From the reference teachings, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

This is a provisional obviousness-type double patenting rejection.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 23-27, 37-39 and 44 *are* rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: the fusion protein of SEQ ID NO:4 and a composition thereof, the specification does not provide reasonable enablement for: **a fusion protein characterized in that it comprises the amino acid sequences of different allergens belonging to the non-specific Lipid Transfer Protein (ns-LTPs) family, in that said sequences lack one or more of the four disulphide bridges present in the sequences of the wild type allergens, at least one in the amino terminal region comprised between amino acid residues 1 and 30 and in that said sequences maintain essentially the same length as the sequences of wild type allergens** of claim 23; characterized in that **the amino acid sequence of each of the allergens is independently mutated by elimination or substitution of one or more cysteine residues involved in the formation of a disulphide bridge** of claim 24; characterized in that it **comprises allergens Parjl and Parj2 of the *Parietaria judaica* species** of claim 25; characterized in that **the amino acid sequence of each of the allergens is independently mutated by elimination or substitution of one or more cysteine residues in positions corresponding to the positions 4, 14, 29, 30, 50, 52, 75 and 91 of the amino acid sequence of Parjl and/or Parj2 allergen** of claim 26; **characterized in that it contains amino acid sequences of Parjl and Parj2 allergens, both independently modified by substitution of**

cysteine residues with Asn, Ser, Thr, lie, Met, Gly, Ala, Val, Gln or Leu residues in positions 29 and 30 or 4, 29 and 30 or 29, 30, 50, 52 of claim 27; a **pharmaceutical composition** comprising **the fusion protein** according to claim 25 and a pharmaceutically acceptable excipient of claim 37 and as applied to claims 38 and 44.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification discloses the generation of the fusion protein of SEQ ID NO:4.

The specification has not adequately disclosed the genus of fusion proteins comprising "the amino acid sequences of different allergens belonging to the non-specific Lipid Transfer Protein (ns-LTPs) family, in that said sequences lack one or more of the four disulphide bridges present in the sequences of the wild type allergens, at least one in the amino terminal region comprised between amino acid residues 1 and 30 and in that said sequences maintain essentially

the same length as the sequences of wild type allergens." The specification has only disclosed Par j 1 and Par j 2, which does not provide sufficient basis for the recitation of any non-specific lipid transfer protein. In addition, the disclosure of Par j 1 and Par j 2 is not sufficient basis for all Par j 1 and Par j 2 proteins, having any variations from wild type, as encompassed by the recitation of "Par j 1" and "Par j 2" proteins.

The specification does not adequately disclose a fusion protein comprising additional sequences added onto the N-and/or C-terminus and having any number of undisclosed mutations. Without guidance in the specification as to what areas to avoid making mutation and/or guidance regarding how to make mutations in designated areas, the resulting mutated polypeptides will have unpredictable activities and binding properties. The art of Blumenthal et al. teaches that a determination of IgE antibody binding to proteins cannot be made a priori based upon antigen structure (PTO-892, Reference W, whole document and page 39 of third full paragraph). Further, mutating certain amino acids may abolish antibody binding altogether as in the case of Colman et al. (PTO-892, Reference X, whole document) and Abaza et al. (PTO-892 page 2, Reference U, whole document), or could increase antibody binding as in the case of Maleki et al. (PTO-892 page 2; Reference V, whole document) which teaches that the denaturation of allergenic proteins (often the result of alteration of disulfide bridges) can increase IgE binding. In either case, the resulting mutants are likely to not be useful in the claimed invention directed to fusions which have therapeutic and diagnostic purpose.

Also at issue is whether or not the fusion proteins disclosed will have pharmaceutical use.

In view of the absence of a specific and detailed description in Applicant's specification of how to effectively use the protein as a pharmaceutical composition as claimed, absence of working examples providing evidence which is reasonably predictive that the claimed composition is effective for in vivo use to treat allergy, and the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed pharmaceutical composition with a reasonable expectation of success.

Substantiating evidence may be in the form of animal tests, which constitute recognized screening procedures with clear relevance to efficacy in humans. See Ex parte Krepelka, 231 USPQ 746 (Board of Patent Appeals and Interferences 1986) and cases cited therein. Ex parte Maas, 9 USPQ2d 1746.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

10. Claims 23-27, 37-39 and 44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of: the fusion protein of SEQ ID NO:4 and a composition thereof.

Applicant is not in possession of: a fusion protein characterized in that it comprises the amino acid sequences of different allergens belonging to the non-specific Lipid Transfer Protein (ns-LTPs) family, in that said sequences lack one or more of the four disulphide bridges present in the sequences of the wild type allergens, at least one in the amino terminal region comprised between amino acid residues 1 and 30 and in that said sequences maintain essentially the same length as the sequences of wild type allergens of claim 23; characterized in that the amino acid sequence of each of the allergens is independently mutated by elimination or substitution of one or more cysteine residues involved in the formation of a disulphide bridge of claim 24; characterized in that it comprises allergens Parjl and Parj2 of the *Parietaria judaica* species of claim 25; characterized in that the amino acid sequence of each of the allergens is independently mutated by elimination or substitution of one or more cysteine residues in positions corresponding to the positions 4, 14, 29, 30, 50, 52, 75 and 91 of the amino acid sequence of Parjl and/or Parj2 allergen of claim 26; characterized in that it contains amino acid sequences of Parjl and Parj2 allergens, both independently modified by substitution of cysteine residues with Asn, Ser, Thr, lie, Met, Gly, Ala, Val, Gln or Leu residues in positions 29 and 30 or 4, 29 and 30 or 29, 30, 50, 52 of claim 27; a pharmaceutical composition comprising the fusion protein according to claim 25 and a pharmaceutically acceptable excipient of claim 37 and as applied to claims 38 and 44.

Applicant has disclosed the fusion protein of SEQ ID NO:4; therefore, the skilled artisan

cannot envision all the contemplated multimer protein possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method.

Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention.

See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 23-28, 37-39 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Columbo et al. (IDS filed on 08/28/2006) in view of Bonura et al. (IDS filed on 08/28/2006) and Pauli et al. (PTO-892; Reference U).

Columbo et al. teaches that Par j 1 and Par j 2 are the two major allergens in Parietaria judaica pollen which are the main cause of allergy in the Mediterranean. Parietaria pollen also contains at least 7 other minor allergens (In particular, second paragraph on page 2780). Par j 1 and Par j 2 allergens exhibit 45% overall homology and 60% homology in the 1-30 region of the proteins known to have one common, discontinuous IgE epitope (In particular, second paragraph on page 2780, first paragraph on page 2784). Colombo et al teaches Par j 1 and Par j2 allergens with substantially the same sequences as 1-102 of SEQ D NO:4 (Parr j2) and 105-243 of SEQ ID NO:4 (Par j I). The reference also teaches loop 1 allergen mutants mutated in amino acids 1-

30 of 1-102 of SEQ D NO:4 (Parr j2) and 105-243 of SEQ ID NO:4 (Par j I) for diagnosis and therapy of pollen allergy (In particular, pages 199-200 'Materials and Methods', sequences in Table 2, whole document). Columbo et al. teaches that mutation of positions C4, C52, C14, C29, C30 and C75 effect structure alanine leads to a loss of IgE binding in this region (In particular, page 2782 first full paragraph). The reference teaches that the development of hypoallergenic molecules with reduced or eliminated IgE binding can be used in allergen therapies (last paragraph), particularly given the importance of these allergens to allergy in the Mediterranean and throughout the world (In particular, second paragraph on page 2780, last paragraph on page 2784). It is noted that 105-243 of SEQ ID NO:4 (Par j I) is the sequence for Par j1 with C4, C29 and C30 mutated to serine and 1-102 of SEQ D NO:4 (Parr j2) is the sequence for Par j 2 with C4, C29 and C30 mutated to serine.

The claimed invention differs from the prior art in the recitation of "a fusion protein characterized in that it comprises the amino acid sequences of different allergens belonging to the non-specific Lipid Transfer Protein (ns-LTPs) family, in that said sequences lack one or more of the four disulphide bridges present in the sequences of the wild type allergens, at least one in the amino terminal region comprised between amino acid residues 1 and 30 and in that said sequences maintain essentially the same length as the sequences of wild type allergens" of claim 23; "characterized in that the amino acid sequence of each of the allergens is independently mutated by elimination or substitution of one or more cysteine residues involved in the formation of a disulphide bridge" of claim 24; "characterized in that it comprises allergens Parjl and Parj2 of the *Parietaria judaica* species" of claim 25; "characterized in that the amino acid sequence of each of the allergens is independently mutated by elimination or substitution of one or more

cysteine residues in positions corresponding to the positions 4, 14, 29, 30, 50, 52, 75 and 91 of the amino acid sequence of Parj l and/or Parj2 allergen" of claim 26; "characterized in that it contains amino acid sequences of Parjl and Parj2 allergens, both independently modified by substitution of cysteine residues with Asn, Ser, Thr, Ile, Met, Gly, Ala, Val, Gln or Leu residues in positions 29 and 30 or 4, 29 and 30 or 29, 30, 50, 52" of claim 27 and "comprising the amino acid sequence SEQ ID NO: 4" of claim 36; "a pharmaceutical composition comprising the fusion protein according to claim 25 and a pharmaceutically acceptable excipient" of claim 37; "the pharmaceutical composition according to claim 37 in the form of a solution, suspension, emulsion, cream, ointment or implant" of claim 38; and :a method for preparation of the pharmaceutical composition according to claim 37, the method comprising mixing said protein in an immunologically active amount with a pharmaceutically acceptable excipient of claim 44."

Bonura et al. teaches that Par j 1 is a major allergens in Parietaria judaica pollen and a main cause of allergy in the Mediterranean. Par j 1 allergen exhibits a high level of homology with the family of non-specific lipid transfer proteins (In particular, page 33, left column). Bonura et al teaches Par j 1 with substantially the same sequences as amino acids 105-243 of SEQ ID NO:4. The reference also teaches mutants that disrupt the cysteine bridges at C14/C29, C30/C75 and C4/C52 by mutation of those cysteine residues with serine for in vivo pharmaceutical use in a pharmaceutically acceptable excipient (In particular, page 37, right column, 'Materials and Methods', whole document). Bonura et al. teaches that mutation of positions C4, C52, C14, C29, C30 and C75 effect structure and leads to a loss of IgE binding in this region (In particular, whole document). The reference teaches that the development of hypoallergenic molecules with reduced or eliminated IgE binding can be used in allergen

therapies (In particular, discussion). It is noted that 105-243 of SEQ ID NO:4 (Par j I) is the sequence for Par j1 with C4, C29 and C30 mutated to serine.

Pauli et al. teaches that dimer and trimer multimer fusion proteins of Bet v 1 in pharmaceutical compositions exhibited reduced skin reactions as determined by in vivo intradermal and skin prick testing (In particular, whole document). The reference also teaches that the dimer and trimer fusion Bet v 1 molecules had retained IgE binding capacity and fold, but microaggregation led to decreased effector cell activation (In particular, page 1081, second full paragraph). The reference suggested that pharmaceutical compositions comprising the multimers for the treatment of allergy should also contain adjuvants to prevent spreading of molecules and to decrease systemic reactions (In particular, page 1082, first paragraph).

It would have been obvious to one of ordinary skill in the art at the time of invention to combine the teachings of Columbo et al. and Pauli et al. produce a multimer fusion protein comprising Par j 1 and Par j 2 to treat allergies because Par j 1 and Par j 2 are the major allergens of Parietaria pollen. It would have been obvious to only include these two allergens since they are the two major allergens and it is desirable to produce pharmaceutical compositions which only comprise the most important allergens without the confounding effects of the seven minor allergens and other components normally present in pollen allergen extracts. By combining Par j 1 and Par j 2 into a single molecule, the molar ratio of the two allergens will be constant, thus providing a controlled dosage of both allergens to patients for optimal immunotherapy use. Because Pauli et al. teaches that dimerization and trimerization of allergens does not lead to a

change in the conformation of the allergen fold and Columbo et al. teaches that the 1-30 IgE epitope of Par j1 and Par j 2 is a conformational, discontinuous epitope, it would also have been obvious to perform mutational analysis at the positions taught by Columbo et al. to generate a Par j1/ Par j2 multimer protein with reduced IgE binding at that epitope. One would be motivated to do this because Columbo et al teaches that it is an important IgE epitope and because the multimer is being generated for in vivo use. It is obvious to combine two compositions which are known to have the same use. One of ordinary skill in the art at the time of invention would have been motivated to perform mutations to arrive at SEQ ID NO 4 for in vivo allergy therapy use, which may further contain an adjuvant because such a molecule would be expected to exhibit reduced IgE binding in addition to reduced effector cell activation when used in vivo to treat allergies. It would be obvious to one of ordinary skill in the art at the time the invention was made to combine the compositions of Columbo et al. and Pauli et al. because it is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

13. Claims 23-28, 37-39 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vrtala et al. (PTO-892; Reference V) in view of Colombo (IDS filed on 08/28/2006) and Bonura et al. (IDS filed on 08/28/2006)

Vrtala et al. teaches recombinant multimeric protein allergen such as dimer and trimer of major birch pollen allergen Bet vl, (In particular, page 2045 and whole document). The recombinant trimer consisting of three covalently linked copies of the allergens is useful for inducing IgG antibodies in vivo (pharmaceutical composition mixed in solution, comprising pharmaceuticaly acceptable excipient) and blocking IgE binding to Bet vl and related allergens, (In particular, abstract and page 2047).

The claimed invention differs from the prior art in the recitation of " a fusion protein characterized in that it comprises the amino acid sequences of different allergens belonging to the non-specific Lipid Transfer Protein (ns-LTPs) family, in that said sequences lack one or more of the four disulphide bridges present in the sequences of the wild type allergens, at least one in the amino terminal region comprised between amino acid residues 1 and 30 and in that said sequences maintain essentially the same length as the sequences of wild type allergens" of claim 23; "characterized in that the amino acid sequence of each of the allergens is independently mutated by elimination or substitution of one or more cysteine residues involved in the formation of a disulphide bridge" of claim 24; "characterized in that it comprises allergens Parjl and Parj2 of the *Parietaria judaica* species" of claim 25; "characterized in that the amino acid sequence of each of the allergens is independently mutated by elimination or substitution of one or more cysteine residues in positions corresponding to the positions 4, 14, 29, 30, 50, 52, 75 and 91 of

the amino acid sequence of Parj l and/or Parj2 allergen" of claim 26; "characterized in that it contains amino acid sequences of Parjl and Parj2 allergens, both independently modified by substitution of cysteine residues with Asn, Ser, Thr, lie, Met, Gly, Ala, Val, Gln or Leu residues in positions 29 and 30 or 4, 29 and 30 or 29, 30, 50, 52" of claim 27 and "comprising the amino acid sequence SEQ ID NO: 4" of claim 36.

Columbo et al. teaches that Par j 1 and Par j 2 are the two major allergens in Parietaria judaica pollen which are the main cause of allergy in the Mediterranean. Parietaria pollen also contains at least 7 other minor allergens (In particular, second paragraph on page 2780). Par j 1 and Par j 2 allergens exhibit 45% overall homology and 60% homology in the 1-30 region of the proteins known to have one common, discontinuous IgE epitope (In particular, second paragraph on page 2780, first paragraph on page 2784). Colombo et al teaches Par j 1 and Par j2 allergens with substantially the same sequences as 1-102 of SEQ D NO:4 (Parr j2) and 105-243 of SEQ ID NO:4 (Par j I). The reference also teaches loop 1 allergen mutants mutated in amino acids 1-30 of 1-102 of SEQ D NO:4 (Parr j2) and 105-243 of SEQ ID NO:4 (Par j I) for diagnosis and therapy of pollen allergy (In particular, pages 199-200 'Materials and Methods', sequences in Table 2, whole document). Columbo et al. teaches that mutation of positions C4, C52, C14, C29, C30 and C75 effect structure alanine leads to a loss of IgE binding in this region (In particular, page 2782 first full paragraph). The reference teaches that the development of hypoallergenic molecules with reduced or eliminated IgE binding can be used in allergen therapies (last paragraph), particularly given the importance of these allergens to allergy in the Mediterranean and throughout the world (In particular, second paragraph on page 2780, last paragraph on page 2784). It is noted that 105-243 of SEQ ID NO:4 (Par j I) is the sequence for

Par j1 with C4, C29 and C30 mutated to serine and 1-102 of SEQ D NO:4 (Parr j2) is the sequence for Par j 2 with C4, C29 and C30 mutated to serine.

Bonura et al. teaches that Par j 1 is a major allergens in Parietaria judaica pollen and a main cause of allergy in the Mediterranean. Par j 1 allergen exhibits a high level of homology with the family of non-specific lipid transfer proteins (In particular, page 33, left column). Bonura et al teaches Par j 1 with substantially the same sequences as amino acids 105-243 of SEQ ID NO:4. The reference also teaches mutants that disrupt the cysteine bridges at C14/C29, C30/C75 and C4/C52 by mutation of those cysteine residues with serine for in vivo pharmaceutical use in a pharmaceutically acceptable excipient (In particular, page 37, right column, 'Materials and Methods', whole document). Bonura et al. teaches that mutation of positions C4, C52, C14, C29, C30 and C75 effect structure and leads to a loss of IgE binding in this region (In particular, whole document). The reference teaches that the development of hypoallergenic molecules with reduced or eliminated IgE binding can be used in allergen therapies (In particular, discussion). It is noted that 105-243 of SEQ ID NO:4 (Par j I) is the sequence for Par j1 with C4, C29 and C30 mutated to serine.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the Par j 1 and Par j2 allergens taught by Colombo and Bonura et al. in the major birch pollen allergen Bet vl dimers and trimers of Vrtala et al because Vrtala et al. teaches that the dimers and trimers are useful for diagnosis and/or treating allergy. Colombo et al. teaches that Par j1 and Pa j 2 can themselves be useful for diagnosis and therapy of Parietaria pollen allergy, so it would be obvious to generated multimer fusions of the allergens for

diagnosis and therapy as well. It would have been obvious to mutate both Par j 1 and Par j 2 in the same cysteine residues since Columbo et al. teaches that Par j 1 and Par j 2 allergens exhibit 45% overall homology and 60% homology in the 1-30 region of the proteins known to have one common, discontinuous IgE epitope.

From the reference teachings, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

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April 12, 2010

Nora M. Rooney

Patent Examiner

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/Nora M Rooney/

Examiner, Art Unit 1644